REMARKS

Applicant has amended claims 1, 3, 4, and 16 and cancelled claims 2, 12, and 21 in this amendment. No new matter has been added by this amendment.

Claims 28-76 were previously withdrawn.

Claims 1, 3-11, 13-20 and 22-27 are now pending in the application.

Claim Objection

The Examiner objected to the limitation of claim 12 that "the caspase inhibitor inhibits one or more cysteinyl aspartic acid proteases". This is not further limiting since caspases are cysteinyl aspartic acid proteases.

Applicants have cancelled claim 12 by this amendment to fully address this objection.

Claims Rejection – 35 USC § 112

Claims 16 and 21 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants respectfully traverse the rejection in regard to claim 21.

The Examiner indicates that "claim 16 includes the limitation that 'the stabilizing media is trehalose'. Trehalose alone is a sugar and while it can be a component of culture media it is not obvious to one of ordinary skill in the art how it can be the only component of the media. This claim will read that the stabilizing media comprises trehalose."

Applicants have amended claim 16 to now recite:

The apparatus of claim 15 wherein the stabilizing media comprises trehalose.

Applicants submit this amendment fully addresses this rejection.

The Examiner further proposes that claim 21 contains the language of "partially evacuated" and that this term is indefinite since it is unclear what is being evacuated from the tube.

Applicants respectfully submit that the term "partially evacuated" means the evacuation of air from the tube thereby reducing the internal pressure in the tube to below atmospheric pressure.

This is fully supported by the following sections of the present specification. For example:

> "Another aspect of the present invention is to provide an evacuated container that is supplied with an effective amount of a stabilizing agent, where the container has an internal pressure sufficiently low to draw a predetermined volume of a biological sample into the container" **(paragraph [0017])**.
>
> "the collection container is evacuated and has a predetermined internal pressure sufficient to draw a predetermined volume of the sample into the collection container" **(claim 53)**.
>
> "For evacuated collection tubes, a tight-fitting, elastomeric plug is generally employed to contain the vacuum during the required storage periods" **(paragraph [0045])**.
>
> "The pressure in chamber **14** is selected to draw a predetermined volume of biological sample into chamber **14**. Preferably, closure **22** is made of a resilient material that is capable of maintaining the internal pressure differential between atmospheric pressure and a pressure less than atmospheric" **(paragraph [0047])**.

Moreover, paragraph [0051] of the present specification describes commercially available evacuated blood collection tubes suitable for use in the present invention.

For these reasons applicants submit claim 21 is definite as defined by 35 USC § 112, second paragraph.

Claims Rejections – 35 USC § 102

(A) Claims 1, 2, 10, 11, 12, 14, 15, 17, 18, and 19 are rejected under 35 U.S.C. 102 (b) as being anticipated U.S. Patent No. 6,184,210 to Keana et al. ("Keana").

(B) Claims 1-7, 10-12, and 20 are rejected under 35 U.S.C. 102 (b) as being anticipated U.S. Patent No. 5,786,227 to Charlton. ("Charlton") with support in light of "Inhibition of etoposide-induced apoptic events by azide" by Willhelm et al. (Immunology Letters, 59 (1997) 53-59).

Of the claims rejected, Claim 1 is independent, claims 2 and 12 have been cancelled, with the remaining claims dependent thereon.

The rejection is respectfully traversed in view of the amendment to claim 1.

Amended claim 1 now recites among other things:

a tube having a reservoir portion for receiving the sample; and
a stabilizing agent in the reservoir of the tube, the agent comprising a caspase inhibitor,
in an amount sufficient to stabilize cells immediately on collection of the sample,
wherein the tube is partially evacuated.

Keana fails to disclose the claimed features of:

a) a tube,
b) immediate stabilization of cells on collection of a sample,
c) that the tube is partially evacuated

Keana discloses a set of novel dipeptides which are inhibitors of apoptic cell death. Keana further discloses the use of multi-well microtiter plates (Example 21) for the culturing of Hela cells, which are used to prove the efficacy of the depeptides as inhibitors of apoptic cell death.

Thus Keana does not anticipate amended claim 1.

Accordingly, claims 10, 11, 14, 15, 17, 18, and 19 being dependent on claim 1, are patentable over the cited reference.

Charlton fails to disclose the claimed feature of a partially evacuated tube.

The MPEP section 2131 on Anticipation — Application of 35 U.S.C. 102(a), (b), and (e) [R-1] states: TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053(Fed. Cir. 1987).

Charlton discloses a fluid collection device for collecting and storing viscous biological samples such as saliva. The device of Charlton includes a concentric tube arrangement having a outer tube with a closed first end and an open second end and an inner tube having a filter at the first end and an open second end, with a cap to seal the open second ends of both tubes after sample collection.

Charlton fails to disclose that the device is evacuated and is completely silent in regards to the internal pressure of the device being less than atmospheric pressure.

The Examiner proposes that Figures 6 and 7 of Charlton show the device is partially evacuated. Applicants respectfully submit that Figures 6 and 7 of Charlton show a plan view of two embodiments of the cap used to seal the device after sample collection and do not give an indication of the internal pressure of the device.

Thus Charlton does not anticipate amended claim 1.

Accordingly, claims 3-7, 10, 11, and 20 being dependent on claim 1, are patentable over the cited references.

Claims Rejections – 35 USC § 103

(C) Claims 1-3, 10-15 and 17-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Keana as applied to claims 1, 2, 10, 11, 12, 14, 15, 17, 18, and 19 in further view of the following arguments.

(D) Claims 1-3 and 10-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Keana as applied to claims 1-3, 10-15 and 17-24 above, and further in view of Carbohydrate Utilization by Cell Cultures (1958) by Eagle et al. ("Eagle").

(E) Claims 1-3, 10-15 and 17-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Keana as applied to claims 1-3, 10-15 and 17-24 above, and further in view of U.S. Patent No. 5,932,473 to Swiderek et al. ("Swiderek").

(F) Claims 1-7, 10-13, 20 and 22-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Charlton as applied to claims 1-7, 10-12, and 20 and in further of arguments below.

(G) Claims 1-13, 20, 22-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Charlton as applied to claims 1-7, 10-13, 20, and 22-27 above and further in view of U.S. Patent No. 5,788,862 to Degen at al. ("Degen").

Of the claims rejected claim 1 is independent, claims 2 and 12 have been cancelled, with the remaining claims dependent thereon.

The rejections are respectfully traversed as to amended claim 1.

The cited references alone or in combination do not teach or suggest a partially evacuated tube having a reservoir portion for receiving a sample, with a stabilizing agent in the reservoir of the tube, the agent comprising a caspase inhibitor, in an amount sufficient to stabilize cells immediately on collection of the sample.

Keana teaches a particular class of dipeptides which have been found to be inhibitors of apoptic cell death. Keana further teaches the in vivo use of these dipeptides for reducing, preventing or treating maladies in which apoptic cell death is either a causative factor or a result.

Keana is completely silent in regard to ex vivo biological sample collection, and the use of partially evacuated tube to collect such a sample and with a stabilizing agent in the reservoir of the tube, the agent comprising a caspase inhibitor, in an amount sufficient to stabilize cells immediately on collection of the sample.

Thus there is no suggestion or teaching in Keana to incorporate a caspase inhibitor into a partially evacuated collection container for the immediate stabilization of cells in a biological sample.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 U.S. 1 (1966).

The focus of the claimed invention is to provide immediate stabilization to an ex vivo blood sample upon collection, in which cells remain unchanged and the occurrence of cell apoptosis within the sample on collection is retarded.

Keana contains no motivation or teaching of the need or importance of immediate stabilization such that one of skill in the art would have not known importance of immediate stabilization on collection of the sample.

In terms of Graham Factors, the Applicant has recognized a problem and discovered that cell apoptosis on collection occurs immediately and to a very significant degree. In fact, the sheer rapidity and severity of cell degradation on collection of a sample was unexpected to those skilled in the art at the time of the invention.

Thus in the absence of hindsight, one skilled in the art would not have been motivated by Keana to look at or for inclusion of a caspase inhibitor in the reservoir of a partially evacuated tube or the need for immediate stabilization on collection of a sample.

In addition, the Examiner cites Eagle, Swiderek, in rejections (D) and (E). However, none of these additional references disclose, teach or suggest a partially evacuated tube having a reservoir portion for receiving a sample, with a stabilizing agent in the reservoir of the tube, the

agent comprising a caspase inhibitor, in an amount sufficient to stabilize cells immediately on collection of the sample.

Charlton teaches a fluid collection device for collecting and storing viscous biological samples such as saliva. The device of Charlton includes a concentric tube arrangement having an outer tube with a closed first end and an open second end and an inner tube having a filter at the first end and an open second end, with a cap to seal the open second ends of both tubes after sample collection.

Charlton fails to teach or even suggest that the device is evacuated and is completely silent in regards to the internal pressure of the device being less than atmospheric pressure. In fact Charlton teaches away from the use of an evacuated tube as the second end of each tube must be open in order facilitate the introduction of the viscous biological samples into the inner tube during collection and the subsequent manipulation of the inner tube required to force the collected viscous sample through filter.

Therefore, one skilled in the art would not have been motivated by Charlton to look at or for the use of a partially evacuated tube.

In addition, the Examiner cites Degen in rejection (G). However, this additional reference fails disclose, teach or suggest a partially evacuated tube having a reservoir portion for receiving a sample, with a stabilizing agent in the reservoir of the tube, the agent comprising a caspase inhibitor, in an amount sufficient to stabilize cells immediately on collection of the sample.

Therefore, Charlton alone or combination with Degen does not render claim 1 obvious. Accordingly, claims 3-11, and 14-27 being dependent on claim 1, are patentable over the cited references.

Conclusion

In view of amendment and remarks herein, applicant submits the claims are patentably distinct over the prior art and allowable in form.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or credit any overpayment to Deposit Account No. 02-1666.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact Applicants agent at the telephone number set forth below.

Respectfully submitted,

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